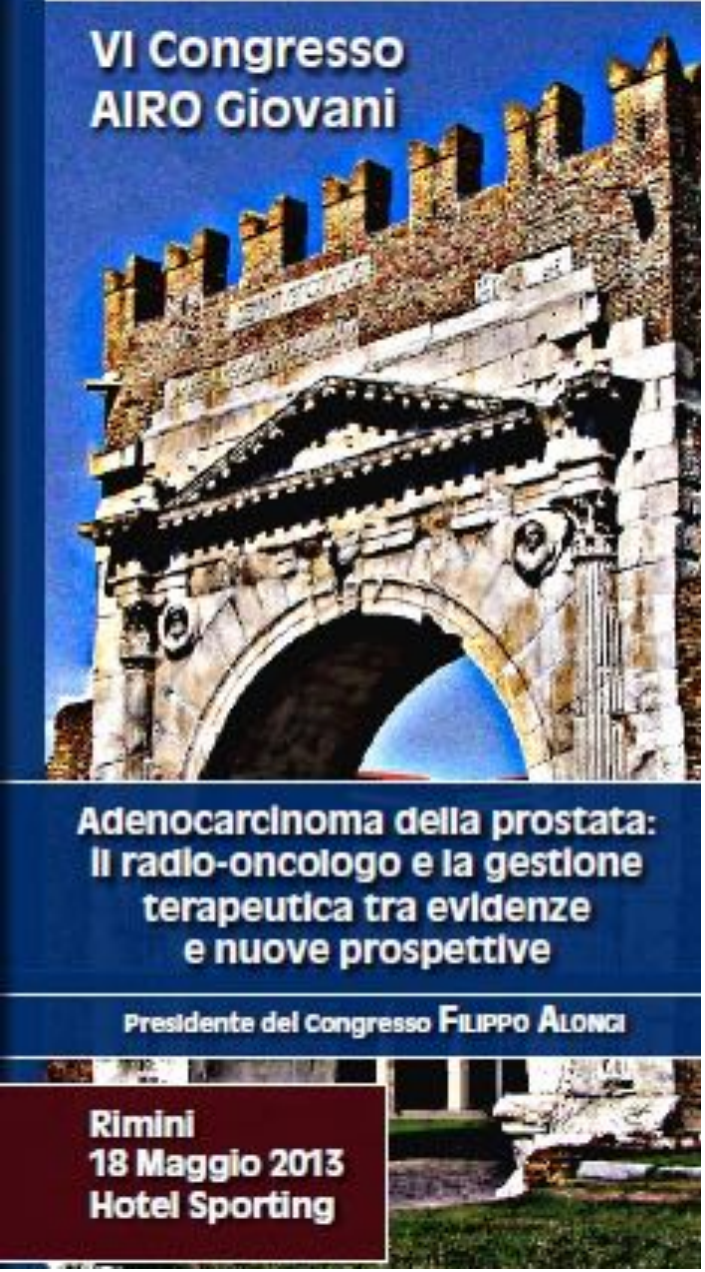

Tumore della prostata localmente avanzato

Ormonoterapia associata a RT radicale: tipo e timing

Rolando M. D'Angelillo

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NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2013
Prostate Cancer

NCCN Guidelines Index
Prostate Table of Contents
Discussion

Risk Class	Definition	ADT+RT
Low risk	T1-2a, GS≤6, PSA ≤10	None
Intermediate Risk	T2b-c, GS=7, PSA =10-20	Neoadj/conc (4-6 mo)
High risk	T3a, GS≥8, PSA>20	Long term neoad/conc/adj (2-3years)
Very High risk	T3b, T4	
Metastatic N1 M0	Any T N+, M0	

Today Agenda

Role of Androgen Deprivation Therapy (ADT) in:

- Intermediate Risk
- High Risk
- Very high risk

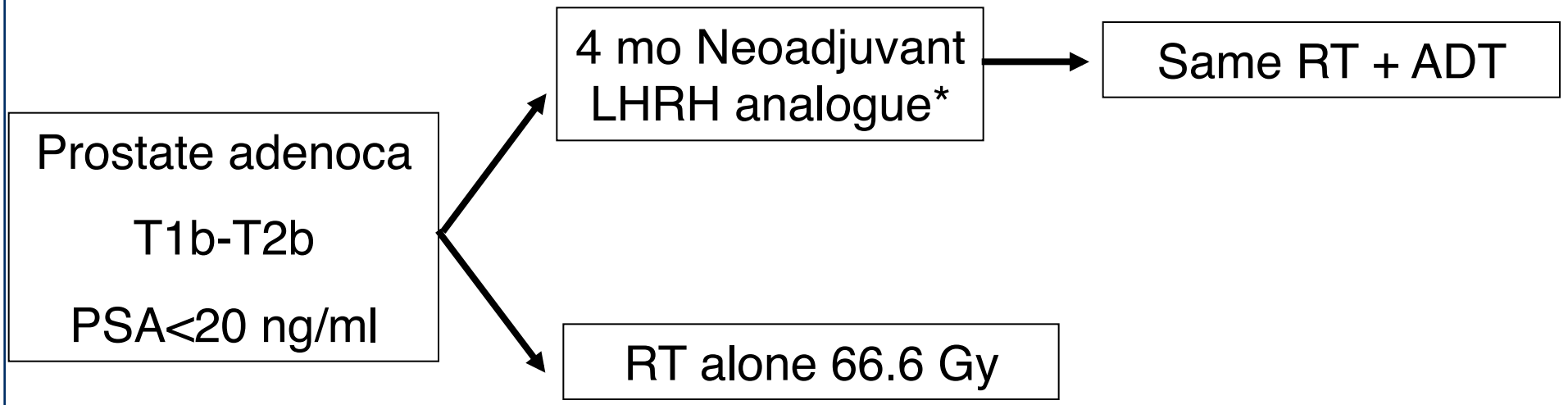
In the era of modern and high dose RT

Today Agenda

Role of Androgen Deprivation Therapy (ADT) in:

- Intermediate Risk
- High Risk
- Very high risk

RTOG 94-08



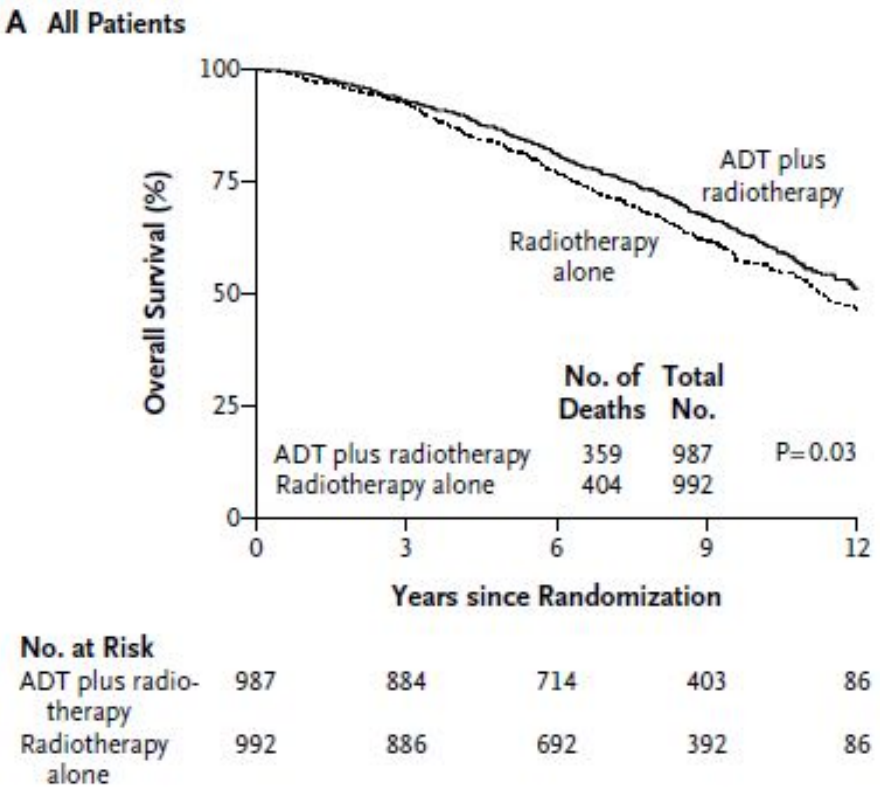
October 94-April 01; 2028 randomized patients

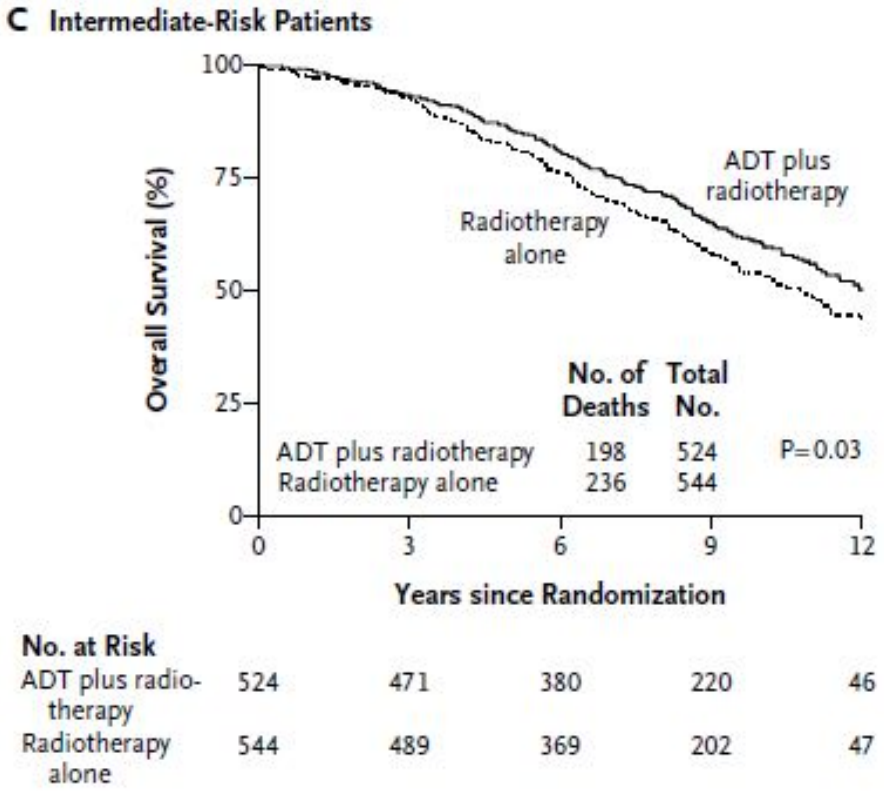
Endpoint: improvement of 8yr OS from 60 to 67%

**Goserelin or Leuprelide*

Jones CU et al, NEJM 365:107-18, 2011

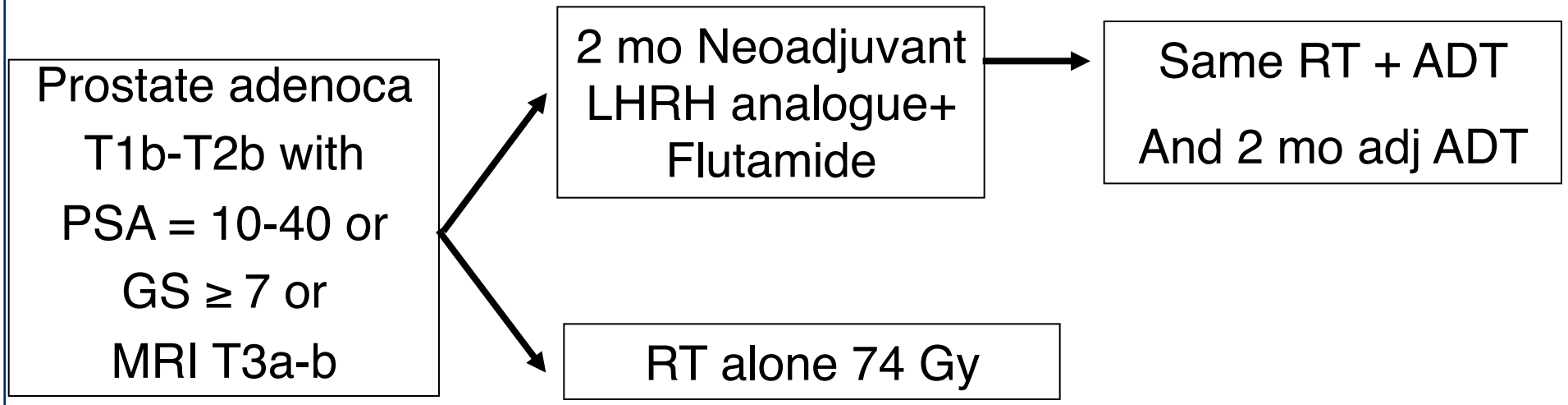
RTOG 94-08





Jones CU et al, NEJM 365:107-18, 2011

Dana Faber Trial (NCT00116220)

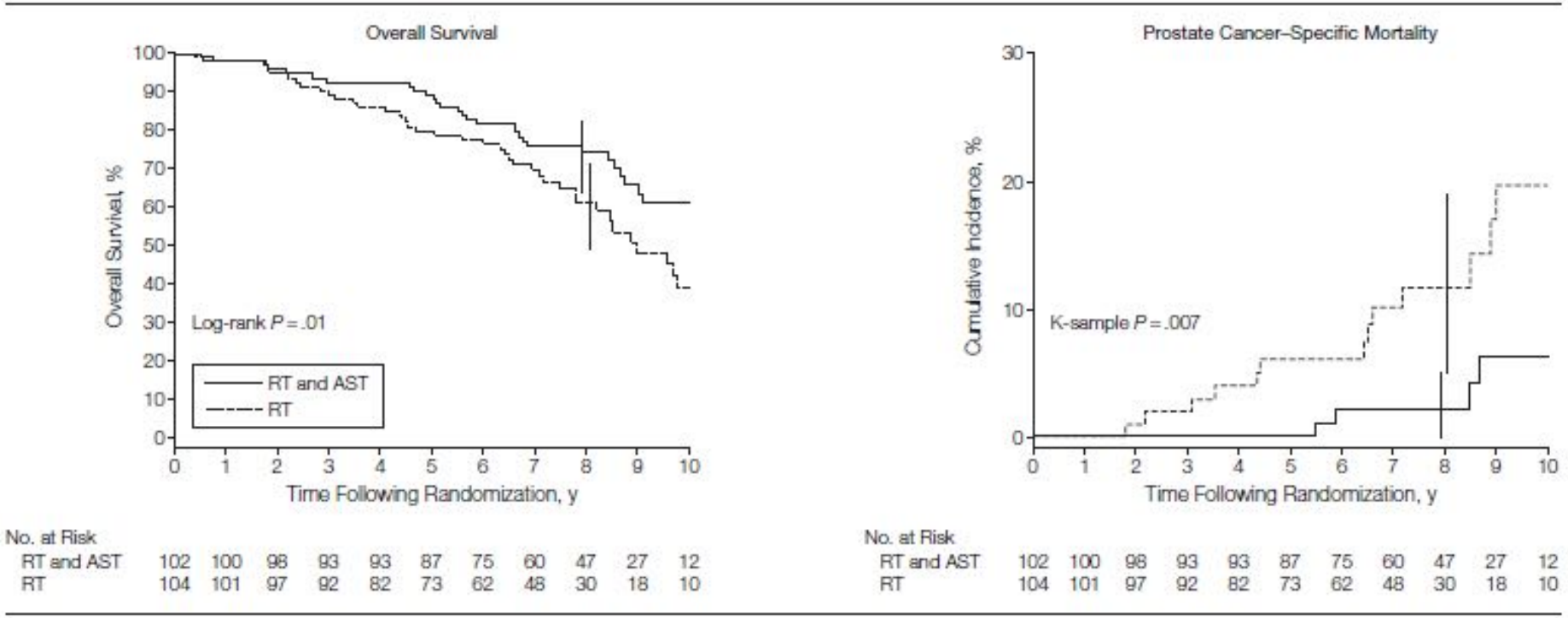


December 95-April 01; 206 randomized patients

Endpoint: improvement of 8yr OS from 60 to 67%

D'Amico AV et al, JAMA.299:289-295, 2008

Dana Faber Trial (NCT00116220)



D'Amico AV et al, JAMA.299:289-295, 2008

ADT Intermediate Risk

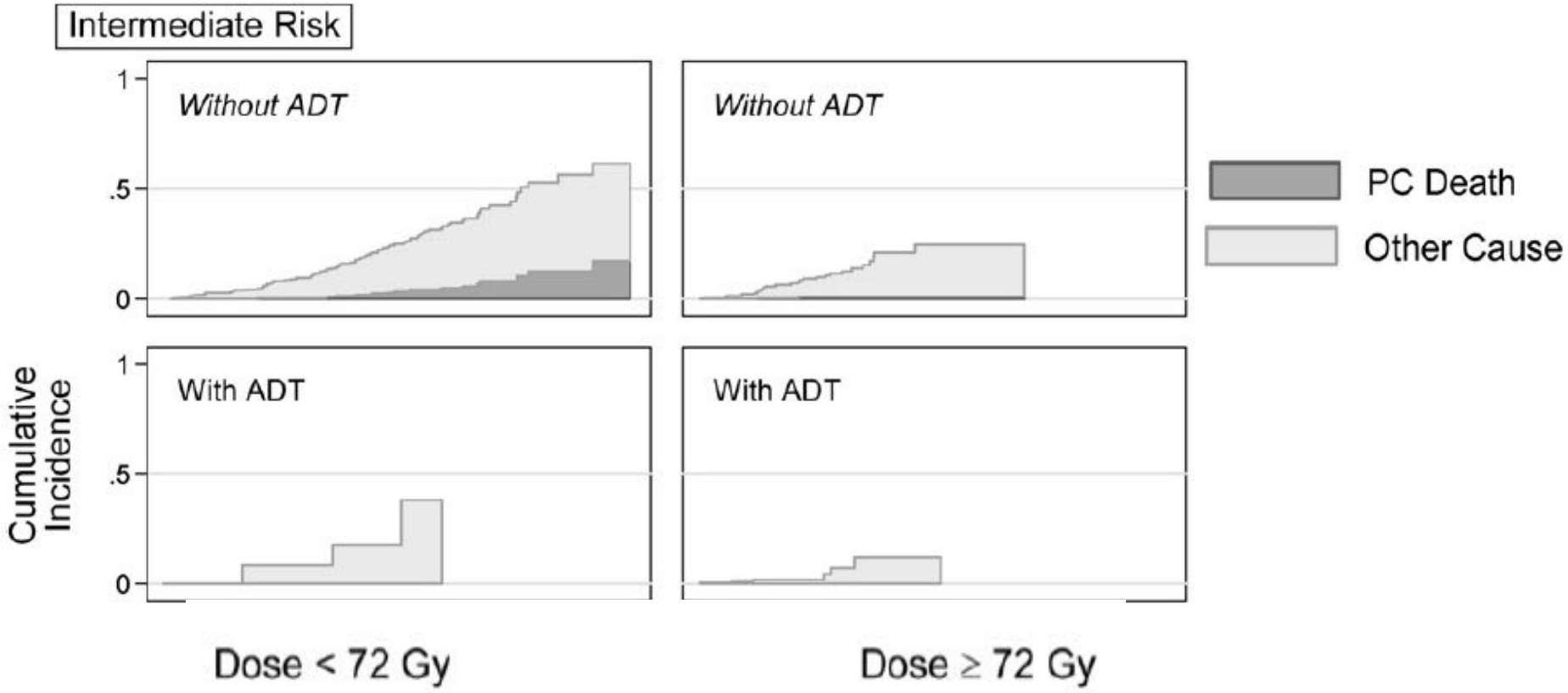
In US improvement in its use from

5% in 1989 to 85% in 2002

But what happens with dose escalation ?

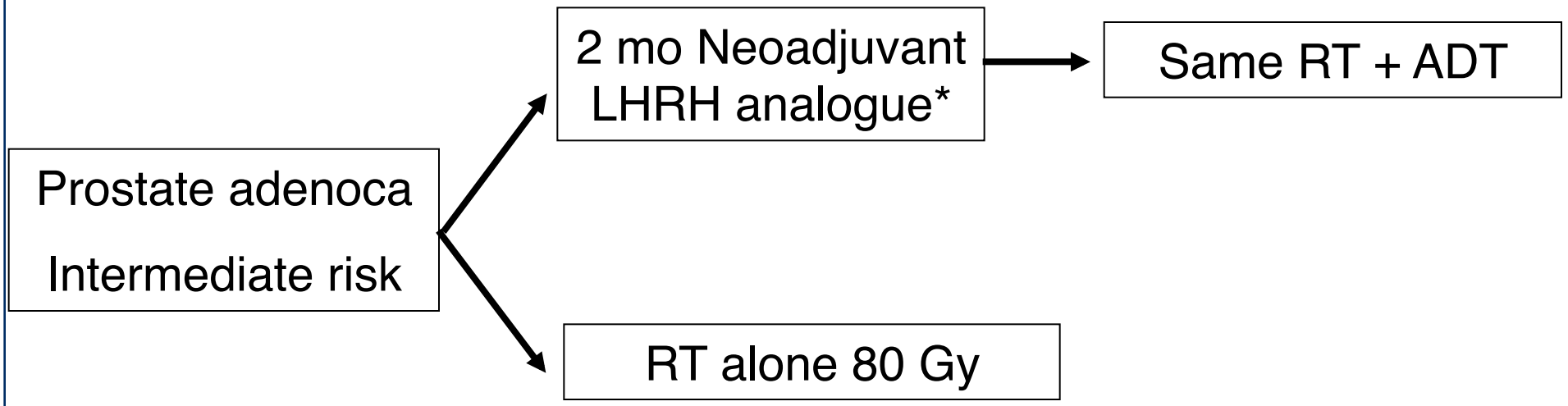
ADT in intermediate risk patients

MD Anderson Dose escalation phase III trial



Kim MM et al, European Journal of Cancer 48:1664– 1671, 2012

GETUG 14, closed for poor accrual



366 randomized patients

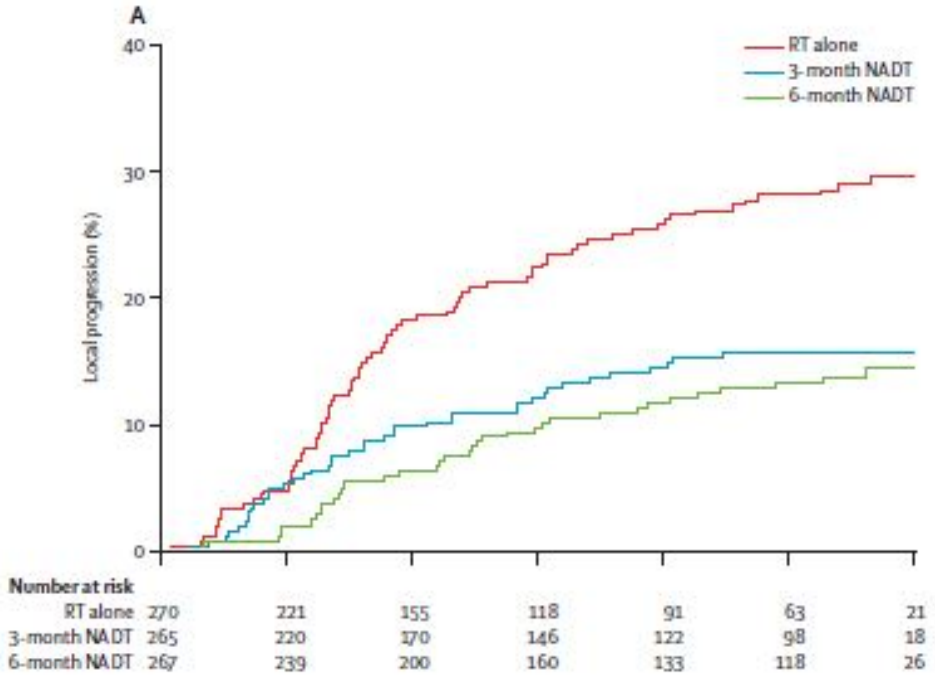
Results: 3 yr bPFS: 97% vs 91% (p=0.04)

Bio and Local Control: 92% vs 86% (p=0.09)

Dubray BM et al, ASCO 2011, abs 4521

ADT in intermediate risk patients

ADT benefit is related to a synergistic local effect:



	Total local progressions	Local progressions at time of death	Total distant progressions	Distant progressions at time of death
RT alone	86	37 (43%)	98	62 (63%)
3-month NADT	53	22 (42%)	79	52 (66%)
6-month NADT	40	9 (23%)	49	31 (63%)

Data are n or n (%). RT=radiotherapy. NADT=neoadjuvant androgen-deprivation therapy.

Table 5: Local and distant progressions at time of prostate-cancer death, by treatment group

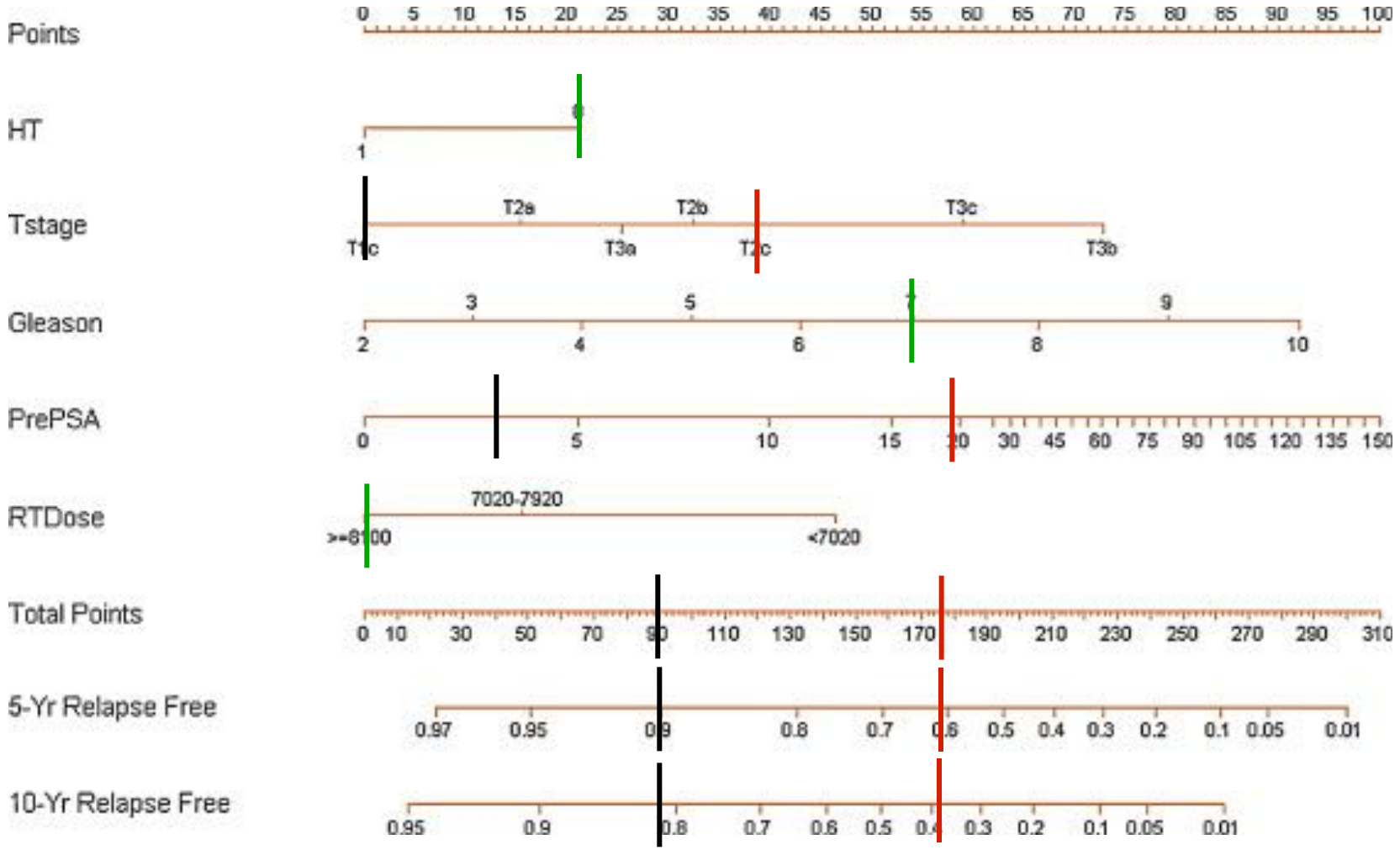
Denham JW et al, Lancet Oncol 12:451-9, 2011

ADT in intermediate risk patients

Heterogeneity and wide range of clinical behaviours:

85 years,	GS=3+4	T1c	PSA=3 ng/ml
45 years,	GS=4+3	T2c	PSA=19 ng/ml

ADT in intermediate risk patients



ADT in intermediate risk patients

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by XXX on pp. x–y of this issue

A New Risk Classification System for Therapeutic Decision Making with Intermediate-risk Prostate Cancer Patients Undergoing Dose-escalated External-beam Radiation Therapy

Zachary S. Zumsteg[a], Daniel E. Spratt[a], Isaac Pei[a], Zhigang Zhang[b], Yoshiya Yamada[a], Marisa Kollmeier[a], Michael J. Zelefsky[a,]*

[a]Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [b]Department of Epidemiology-Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Zumsteg ZS JW et al, Eur Urol 2013 in press

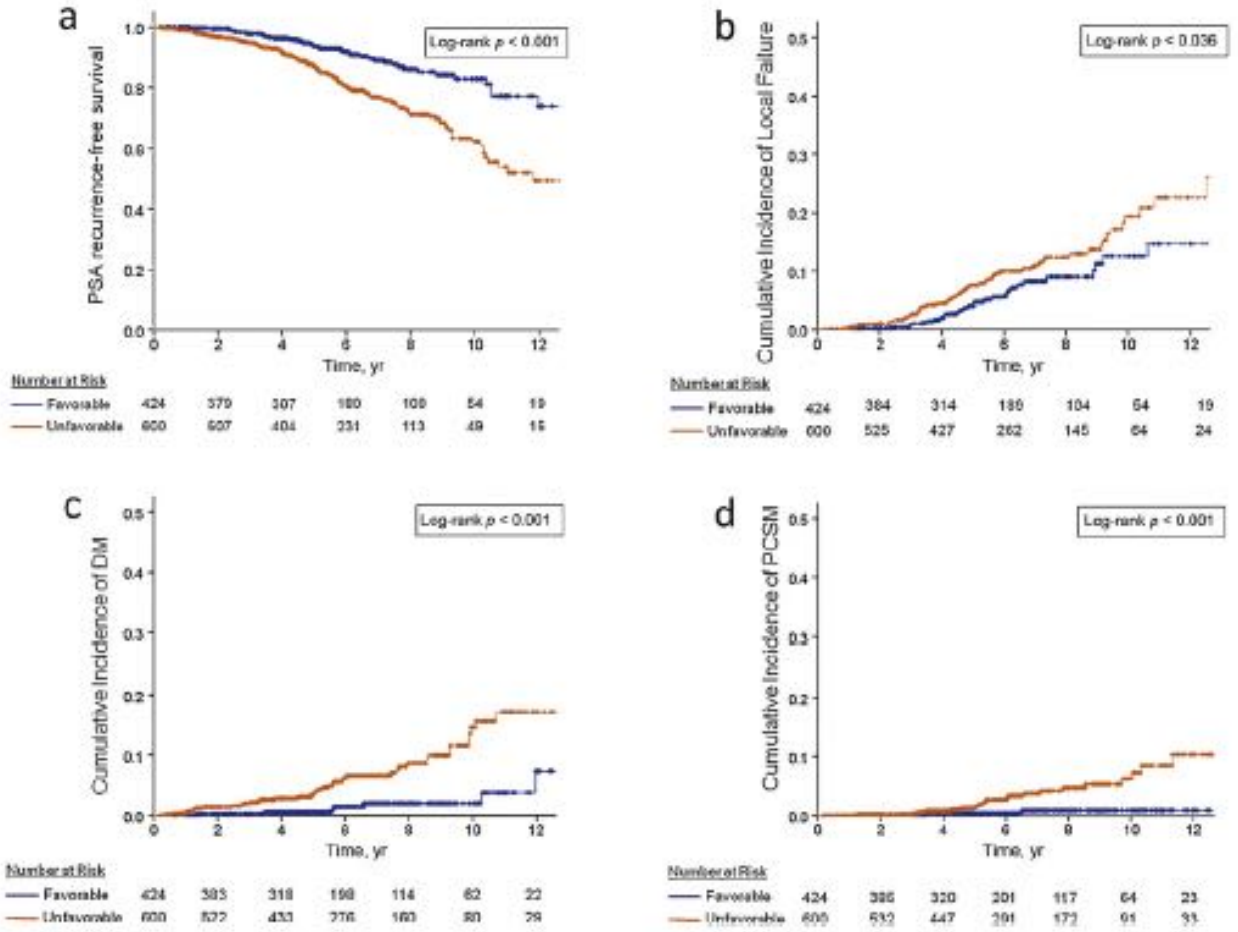
ADT in intermediate risk patients

1024 patients treated with EBRT ≥ 81 Gy

Favorable	Unfavorable
One intermediate risk factor	Several intermediate risk factors
Gleason score 3+4 or less	Gleason score 4+3
<50% positive biopsy cores	≥50% positive biopsy cores

Zumsteg ZS JW et al, Eur Urol 2013 in press

ADT in intermediate risk patients



Zumsteg ZS JW et al, Eur Urol 2013 in press

ADT in intermediate risk patients

Stratify patients:

- MSKCC algorithm
- Nomograms

Favorable disease → High dose **RT alone**

Unfavorable disease → **RT + Neo/Conc ADT**

Today Agenda

Role of Androgen Deprivation Therapy (ADT) in:

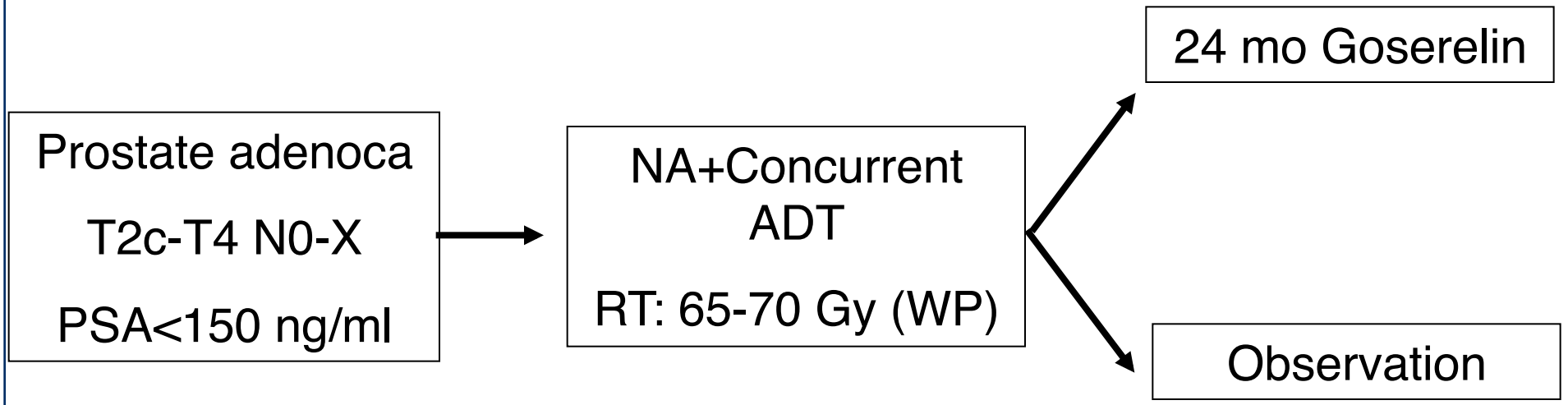
- Intermediate Risk
- High Risk
- Very high risk

ADT in high risk patients

Randomized trials:

- RTOG 92-02
- EORTC 22863
- EORTC 22961
- RTOG 85-31

RTOG 92-02



June 92-April 95; 1521 eligible patients

Endpoint: improvement of 5yr DFS from 40 to 50%

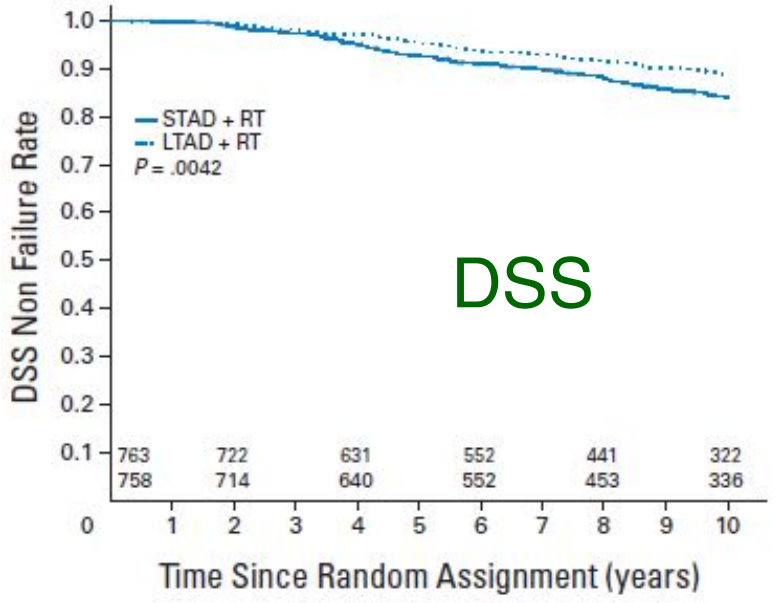
Event time: from randomization

Horwitz EM et al, J Clin Oncol 26:2497-2504, 2008

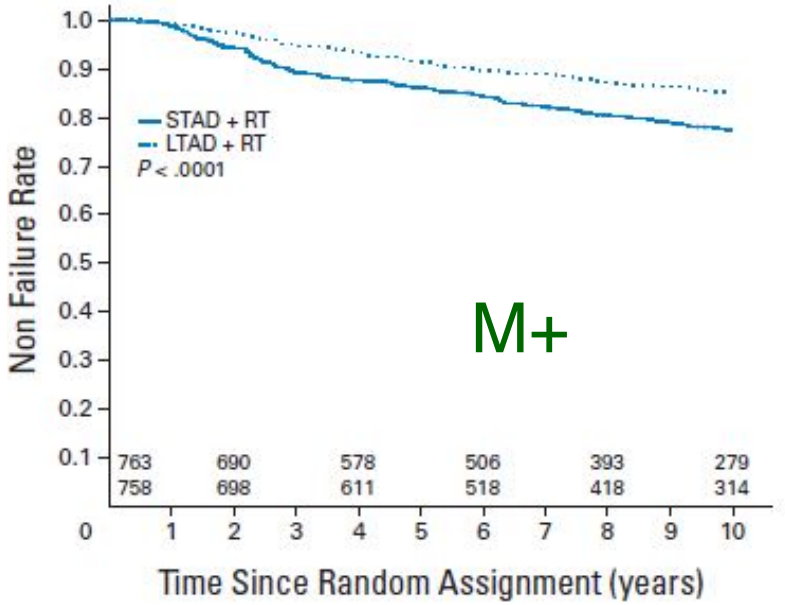
RTOG 92-02

Table 3. 10-Year Treatment Outcomes for All Eligible Patients

Outcome	STAD + RT (n = 763)			LTAD + RT (n = 758)			Log-Rank χ^2 Test *P*
	No. of Failures	Estimated Rate	95% CI	No. of Failures	Estimated Rate	95% CI	
Disease-free survival	653	13.2	11 to 16	571	22.5	19 to 26	< .0001*
Overall survival	351	51.6	48 to 55	330	53.9	50 to 58	.3590
Disease-specific survival	116	83.9	81 to 87	80	88.7	86 to 91	.0042*
Local progression	166	22.2	19 to 25	90	12.3	10 to 15	< .0001*
Distant metastasis	167	22.8	20 to 26	107	14.8	12 to 17	< .0001*
Biochemical failure	513	68.1	65 to 71	384	51.9	48 to 55	< .0001*

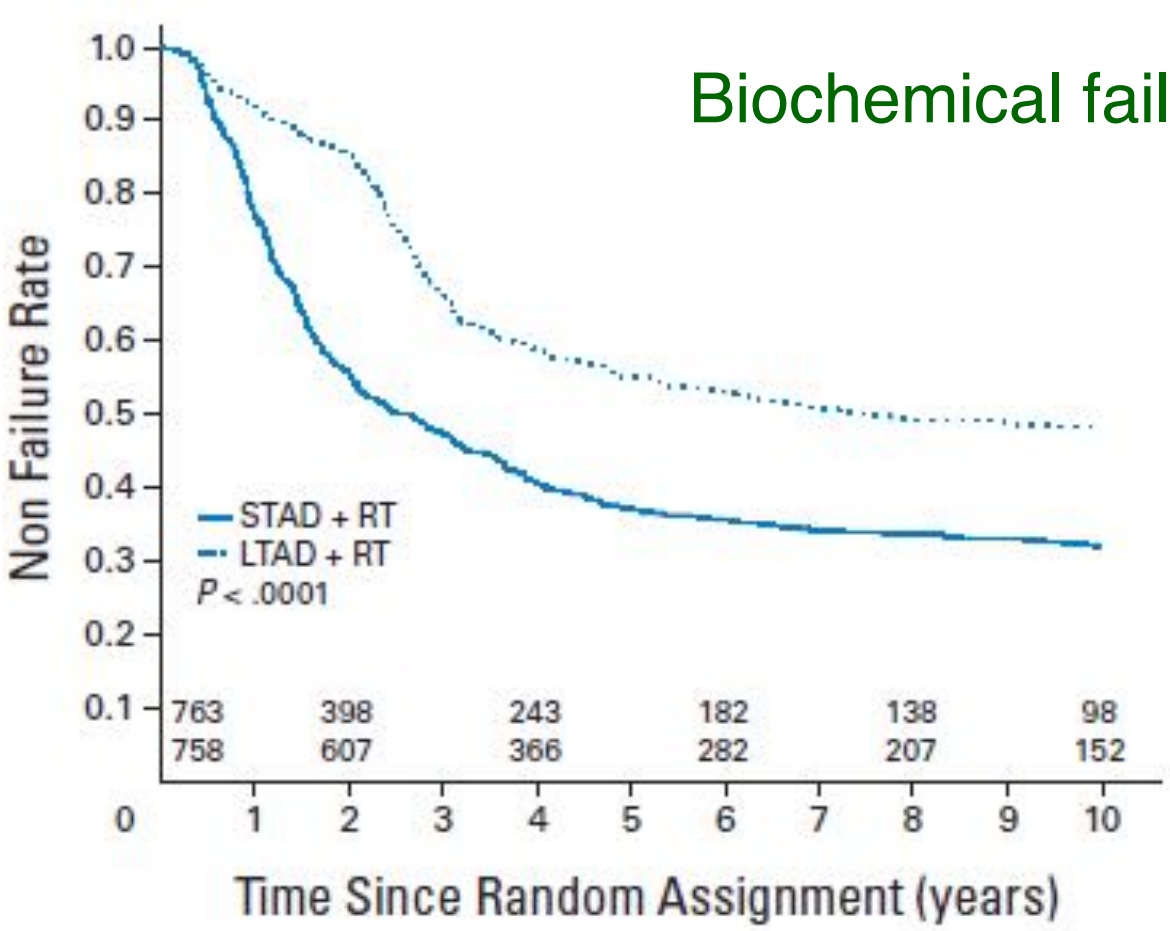


DSS



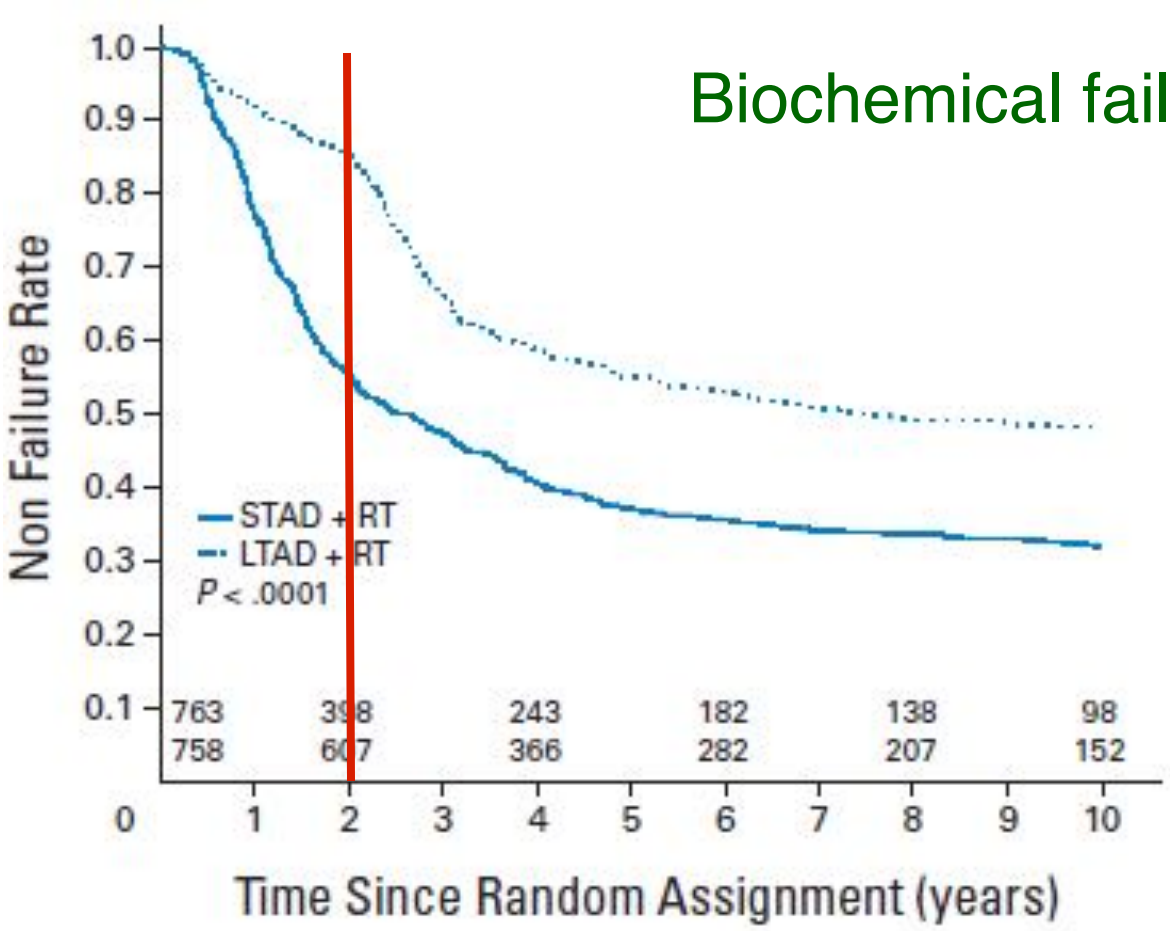
M+

RTOG 92-02



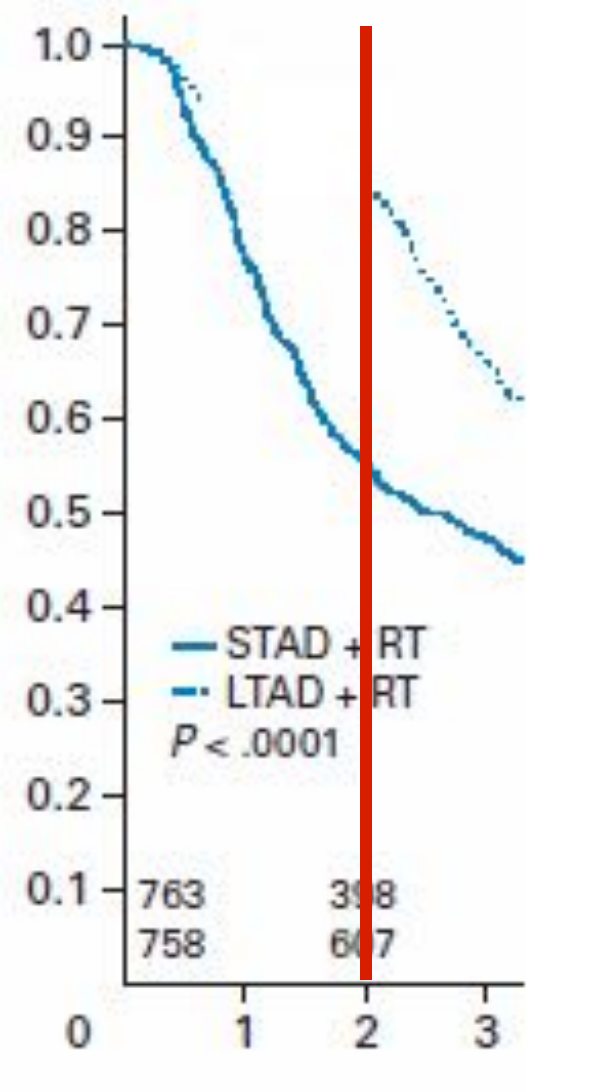
Horwitz EM et al, J Clin Oncol 26:2497-2504, 2008

RTOG 92-02



Horwitz EM et al, J Clin Oncol 26:2497-2504, 2008

RTOG 92-02



Could ADT in this setting just delay disease progression ?

Horwitz EM et al, J Clin Oncol 26:2497-2504, 2008

EORTC 22863

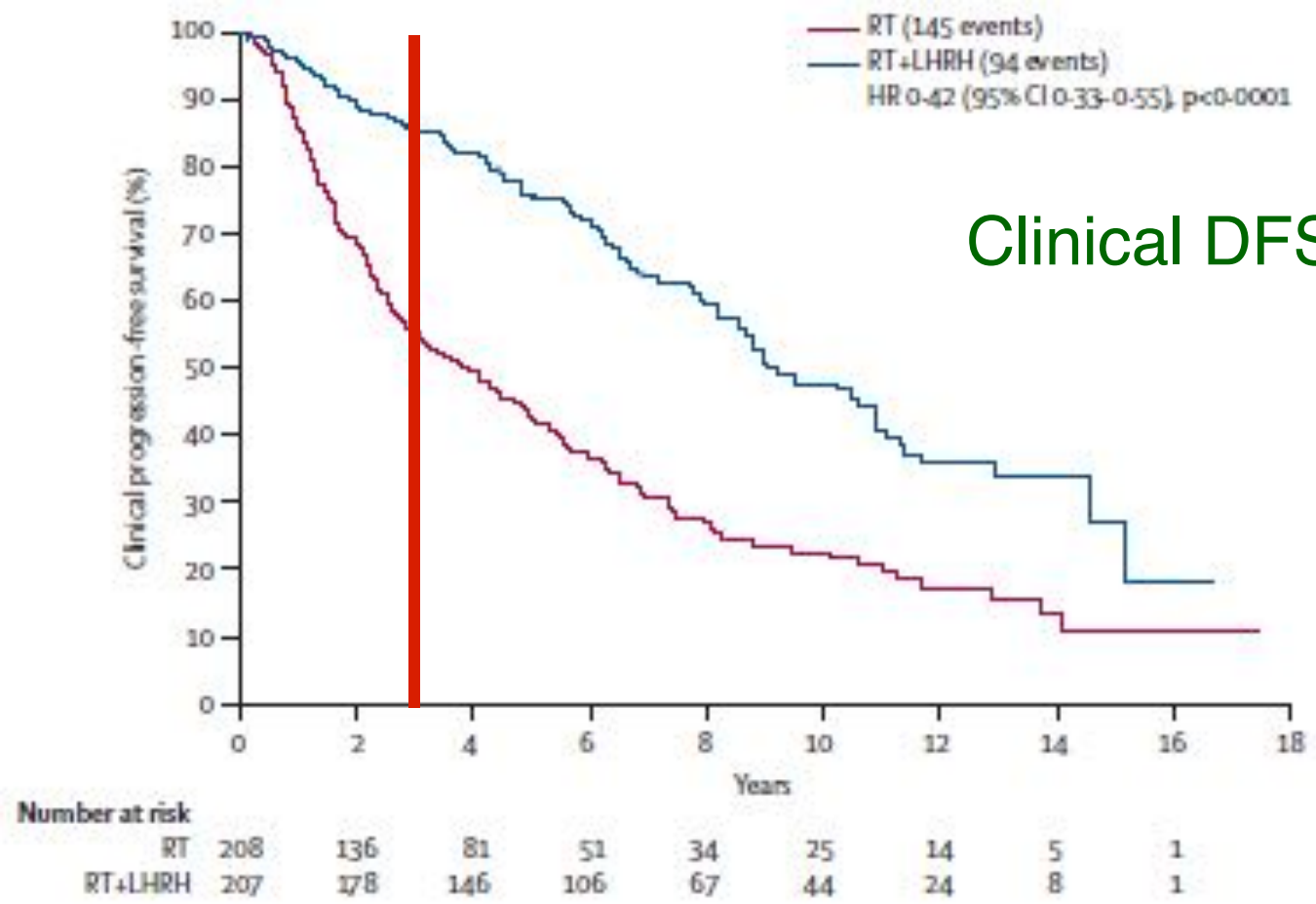
May 87-Oct 95; 415 eligible patients

Endpoint: **HR=0.65 for clinical** DFS

Event time: from randomization

Bolla M et al, Lancet Oncol 11:1066-73, 2010

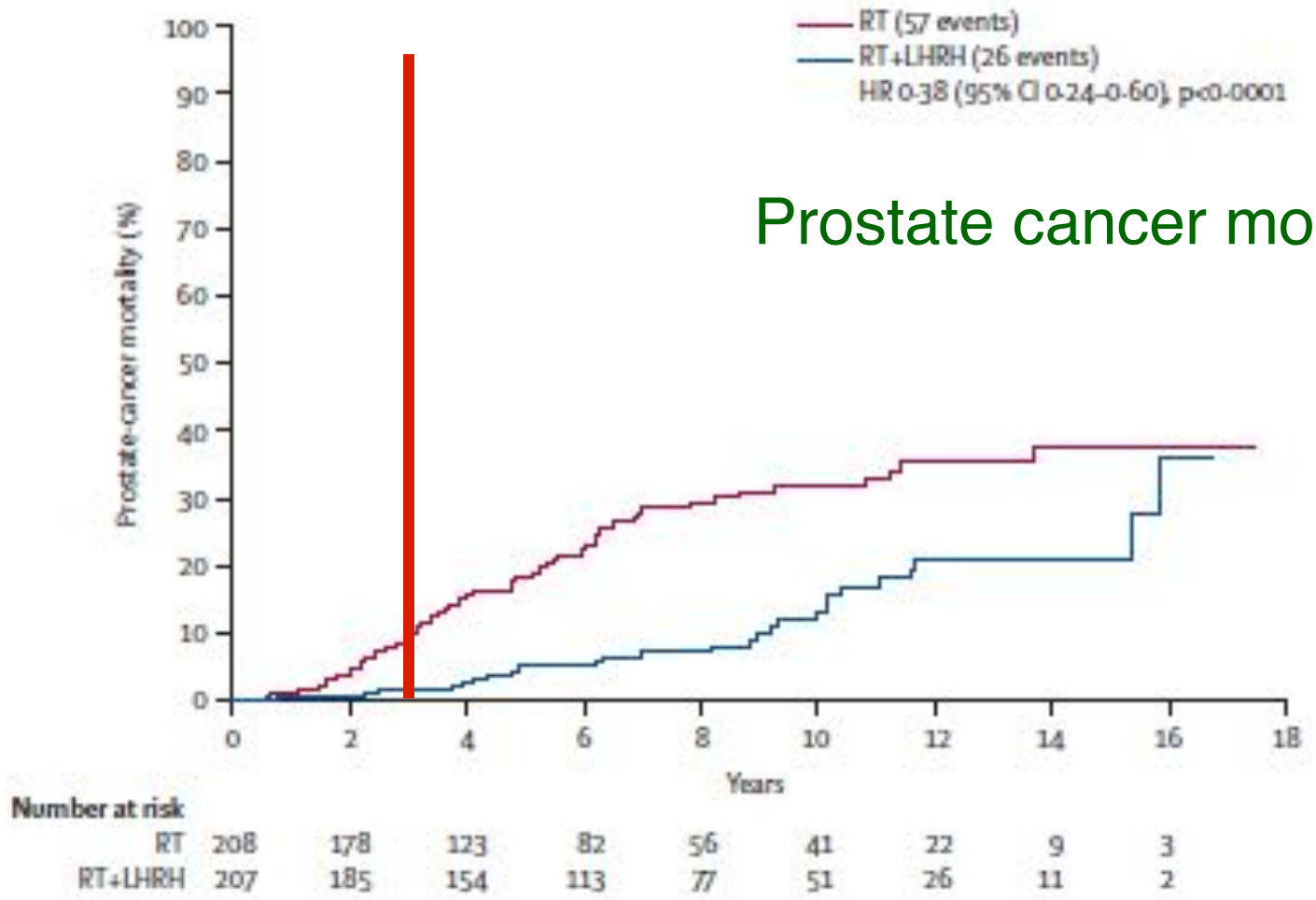
EORTC 22863



Clinical DFS

Bolla M et al, Lancet Oncol 11:1066-73, 2010

EORTC 22863



Prostate cancer mortality

Bolla M et al, Lancet Oncol 11:1066-73, 2010

ADT in high risk patients

Thus, data on 3-years ADT are more consistent than 2yr ADT?

EORTC 22961

April 97-November 01; 970 randomized patients

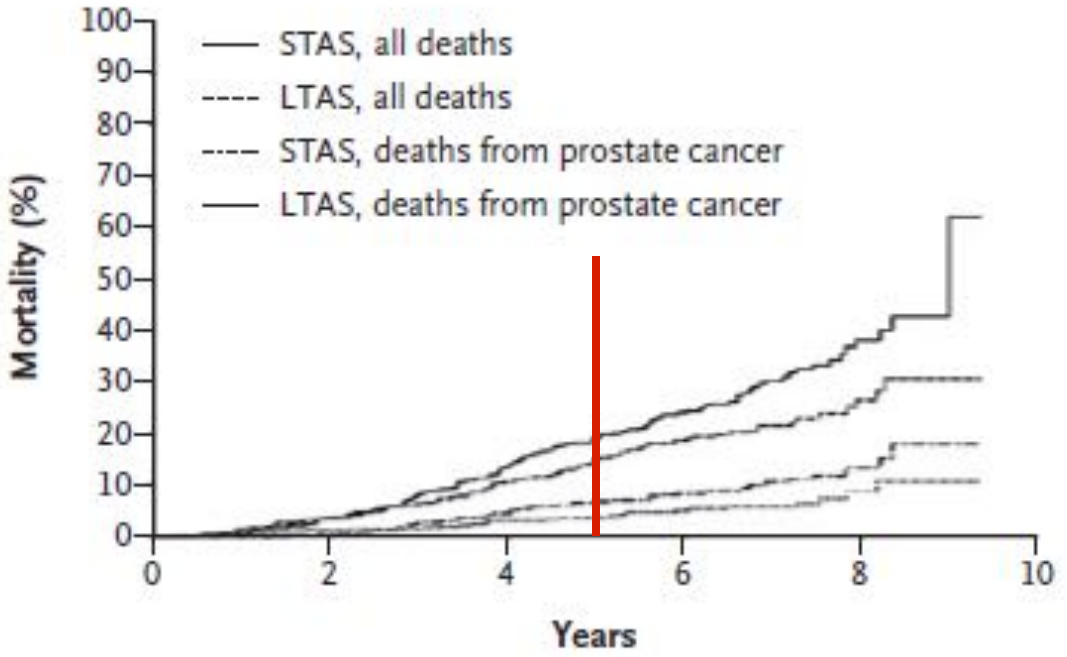
Endpoint: **non-inferiority trial, Prostate cancer mortality**

Event time: from randomization

Bolla M et al, NEJM 360:2516-27, 2009

EORTC 22961

5-years PCM
Long ADT: 4.7%
Short ADT: 3.2%
p=0.002



No. at Risk						No. of Events
STAS, all deaths	483	454	388	231	43	132
LTAS, all deaths	487	454	407	249	50	98
STAS, deaths from prostate cancer	483	454	388	231	43	47
LTAS, deaths from prostate cancer	487	454	407	249	50	29

Bolla M et al, NEJM 360:2516-27, 2009

ADT in high risk patients

Why so confusing results?

How much these data reflect our patients in

daily clinical practise?

ADT in high risk patients

Different patient population

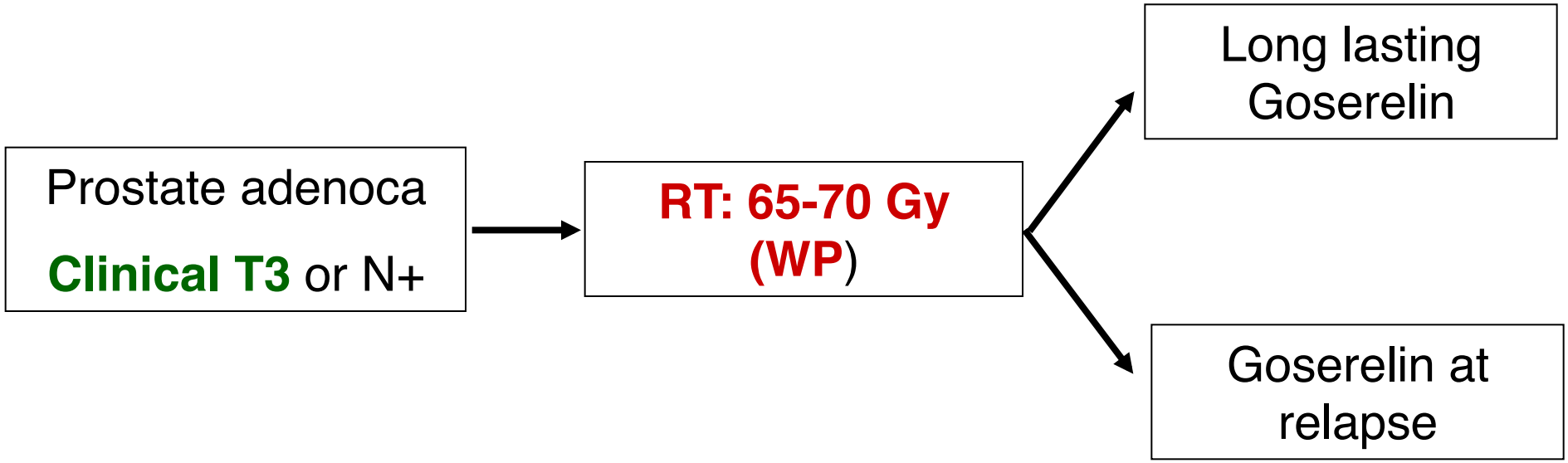
Patients' characteristics	RTOG 92-02 (1992-1995)	EORTC 22863 (1987-1995)
Clinical stage		
T2	45%	10%
T3-T4	**55%**	**90%**
Gleason score		
≤7	76%	67%
≥8	**14%**	**33%**
PSA @ diagnosis		
>20 ng/ml	**33%**	**58%**

ADT in high risk patients

Different patient population

Patients' characteristics	RTOG 85-31 (1987-1992)	EORTC 22863 (1987-1995)
Clinical stage		
T2	Not reported	10%
T3-T4		**90%**
Gleason score		
≤7	68%	67%
≥8	**32%**	**33%**
PSA @ diagnosis		
>20 ng/ml	**Not mandatory**	**58%**

RTOG 85-31

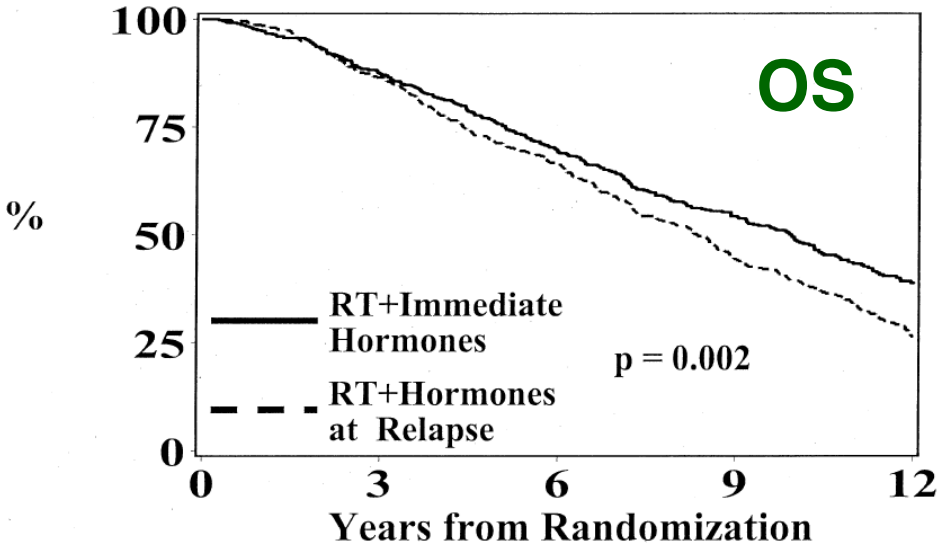


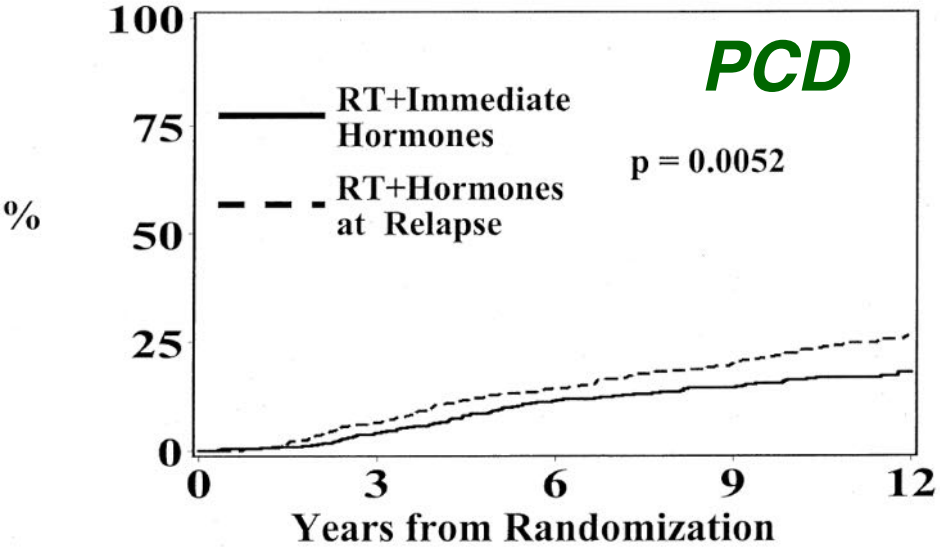
Jan 87-Dec 92; 977 enrolled patients

Endpoint: **not reported**

Pilepich MV et al, Int J Radiat Oncol Biol Phys 61:1285-90, 2005

RTOG 85-31

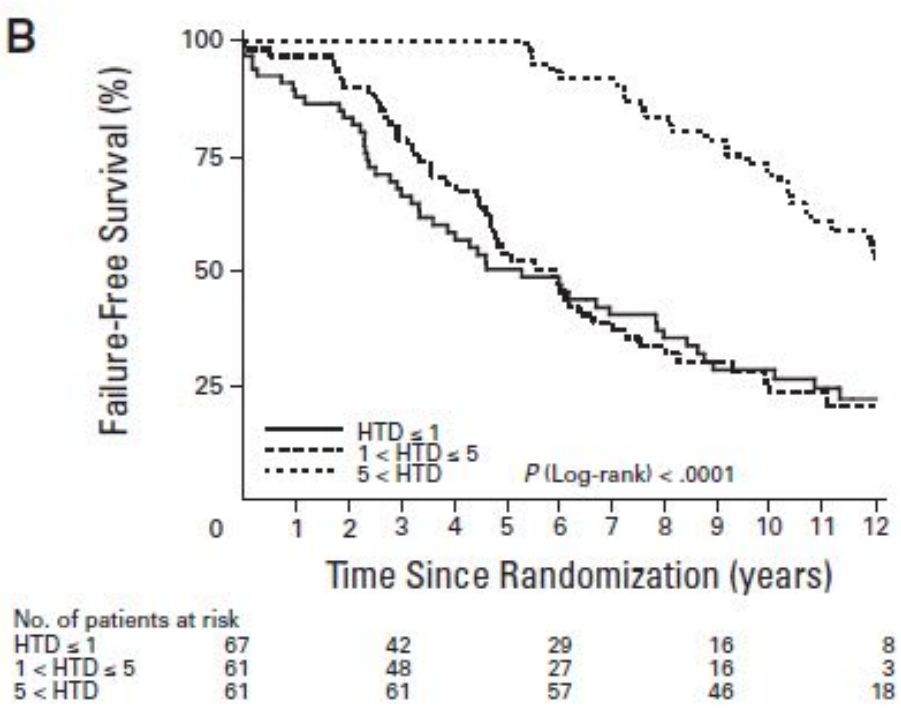


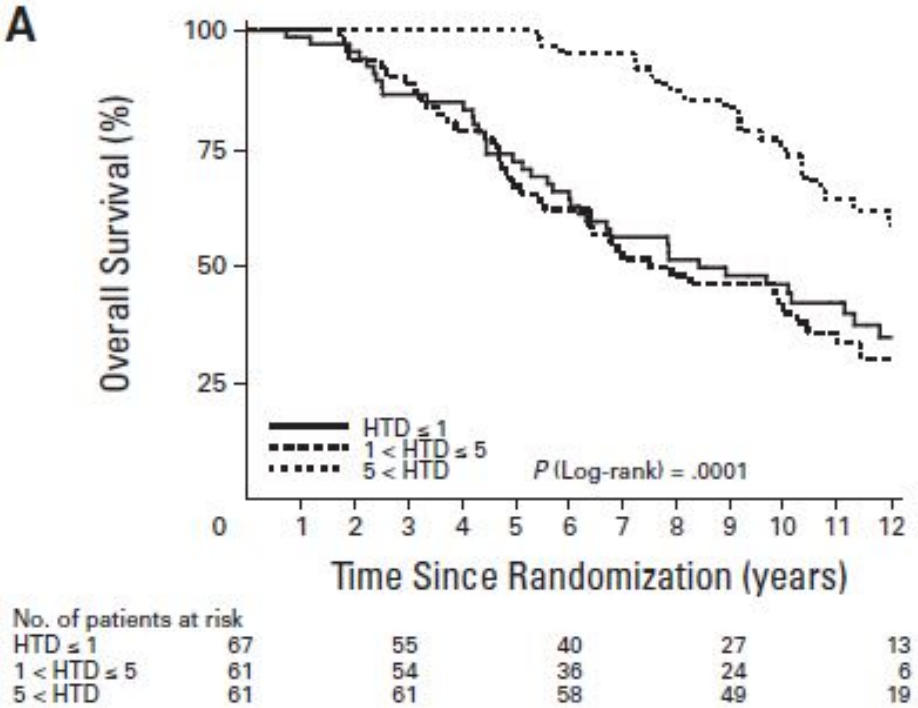


Pilepich MV et al, Int J Radiat Oncol Biol Phys 61:1285-90, 2005

RTOG 85-31

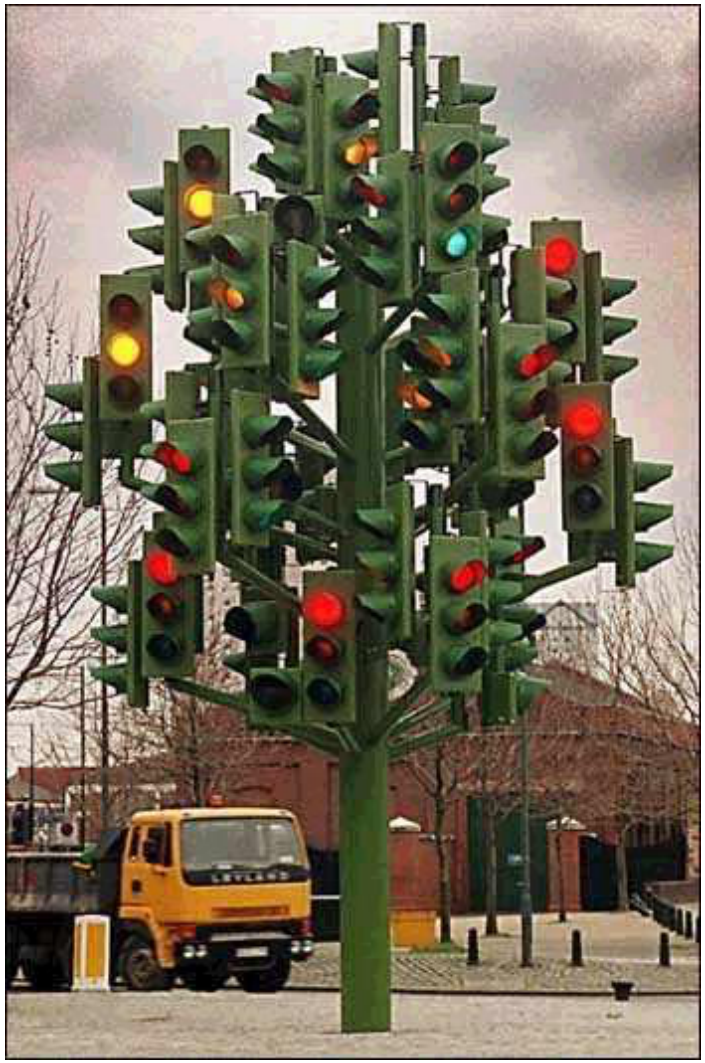
Update on 189 patients in Long Lasting arm





Pilepich MV et al, Clin Oncol 27:2137-2143, 2009

ADT in high risk patients



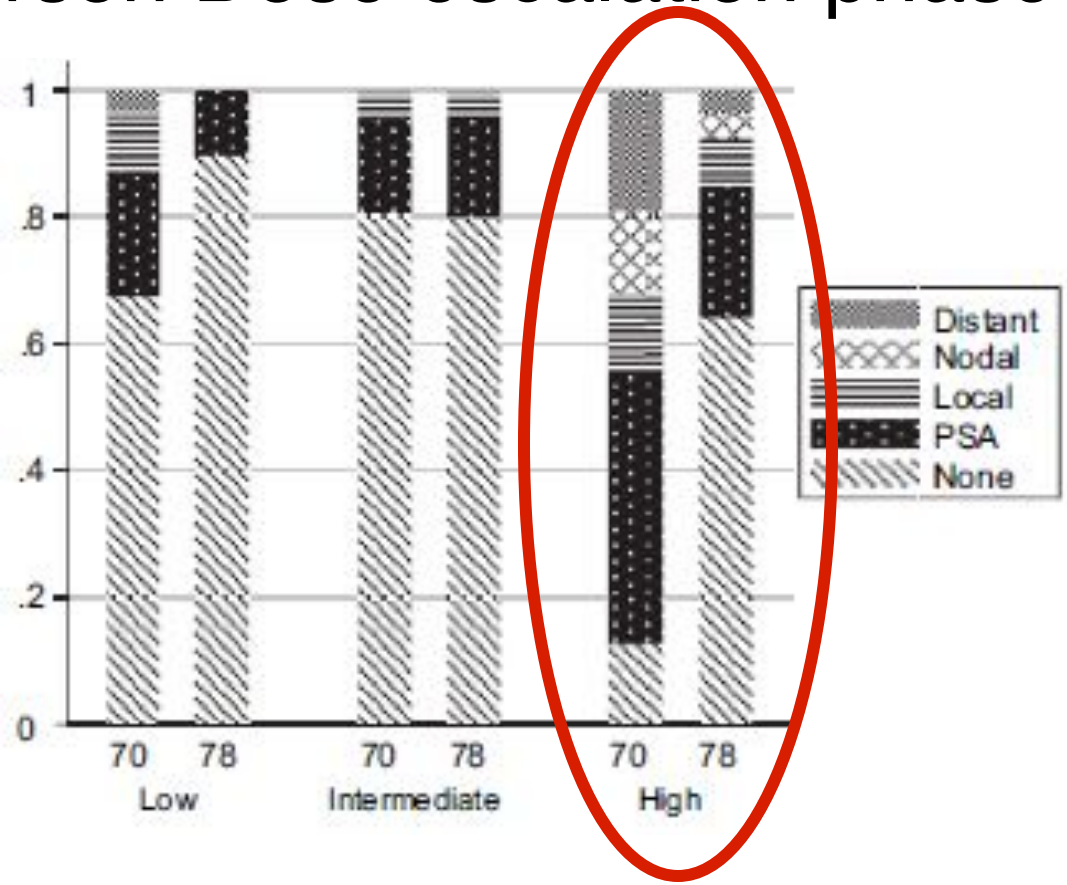
Thus, 2 years, 3 years, 5 years, long lasting ADT in these patients?

Or no ADT if High Dose RT is applied ?

Or, no RT and Long lasting ADT?

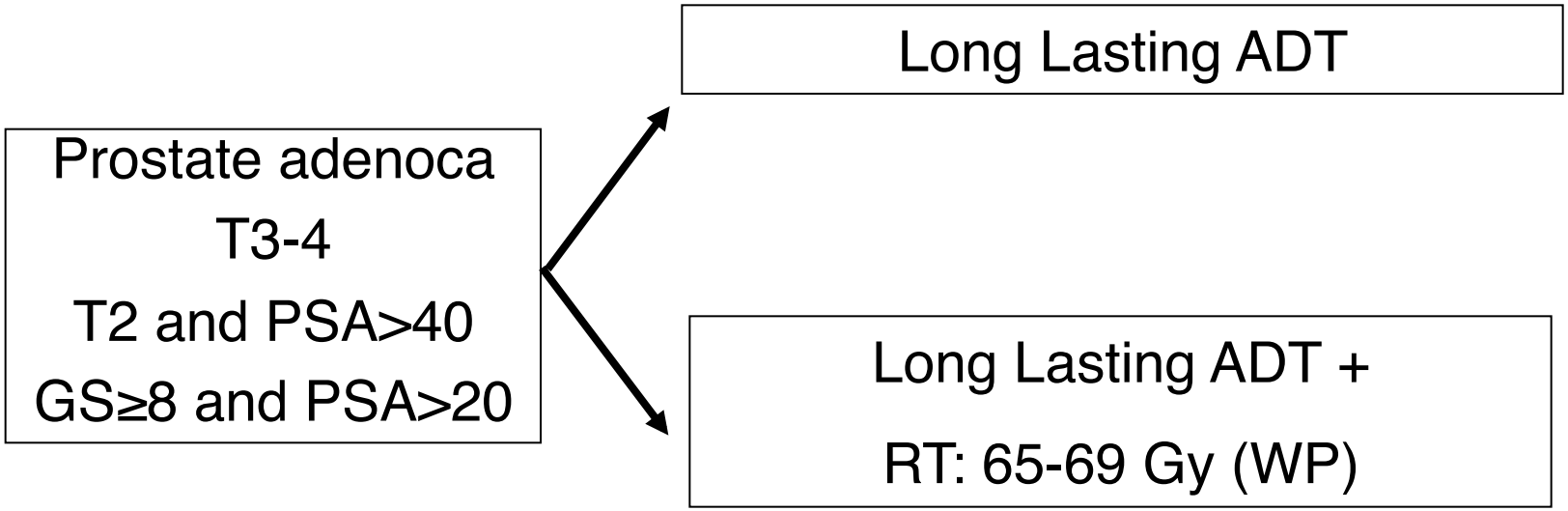
ADT in high risk patients

MD Anderson Dose escalation phase III trial



Kuban DA et al, Int J Radiat Oncol Biol Phys 79:1310-7, 2011

Canada-UK Trial PR.3/PR7



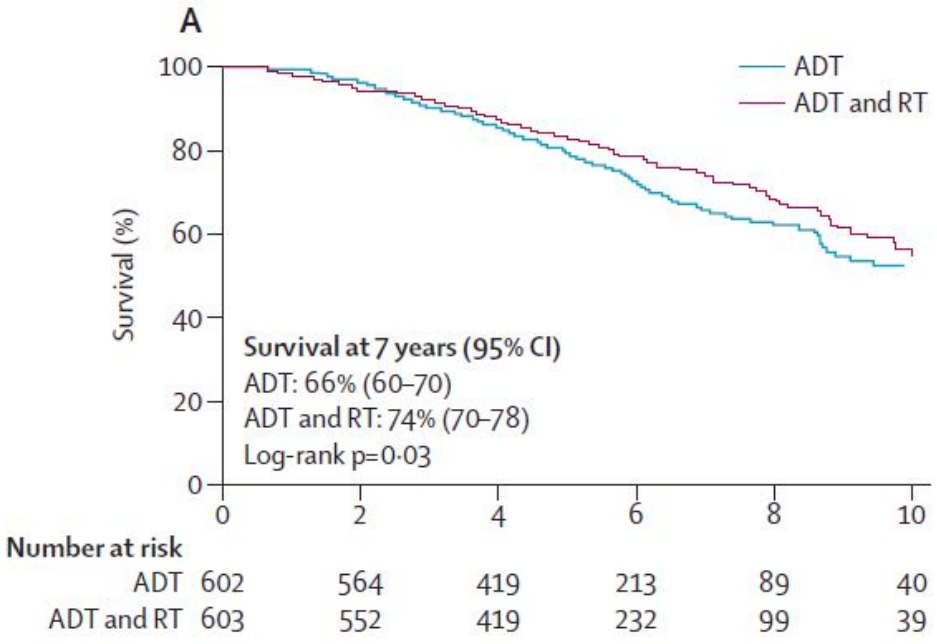
March 95-August 05; 1205 randomized patients

Endpoint: **improvement in 10 yr Survival (57% ADT only)**

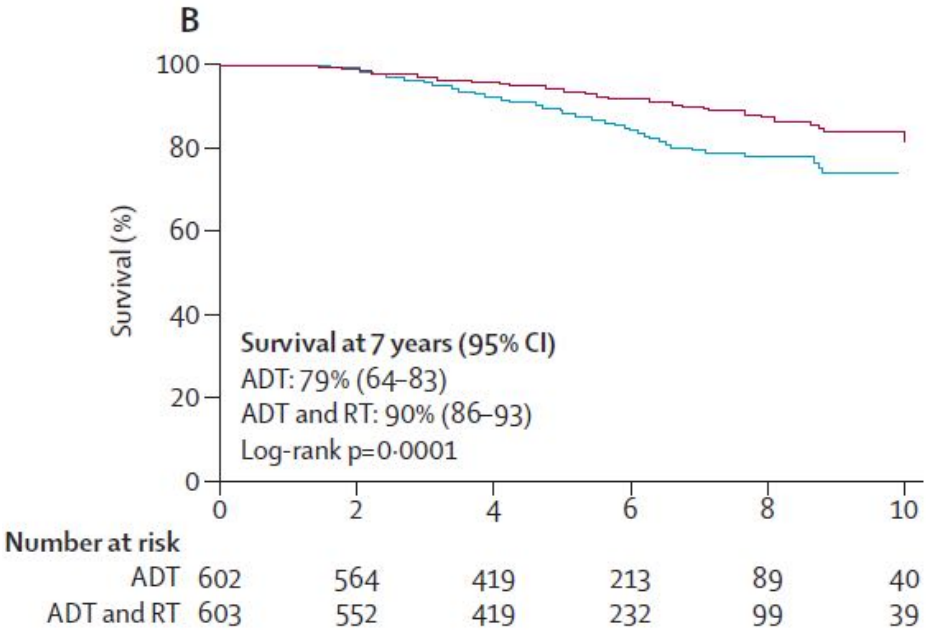
Warde P et al, Lancet 378:2104-11, 2011

Canada-UK Trial PR.3/PR7

Overall Survival



Disease Specific Survival



Warde P et al, Lancet 378:2104-11, 2011

ADT in high risk patients

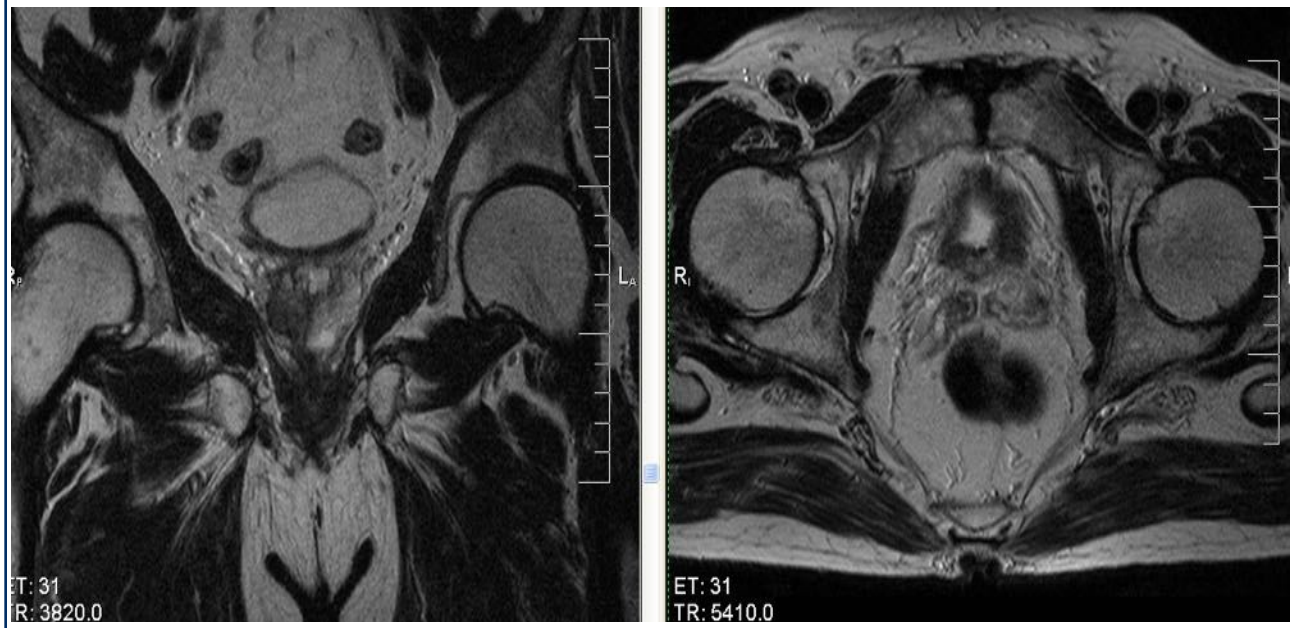
My personal belongings

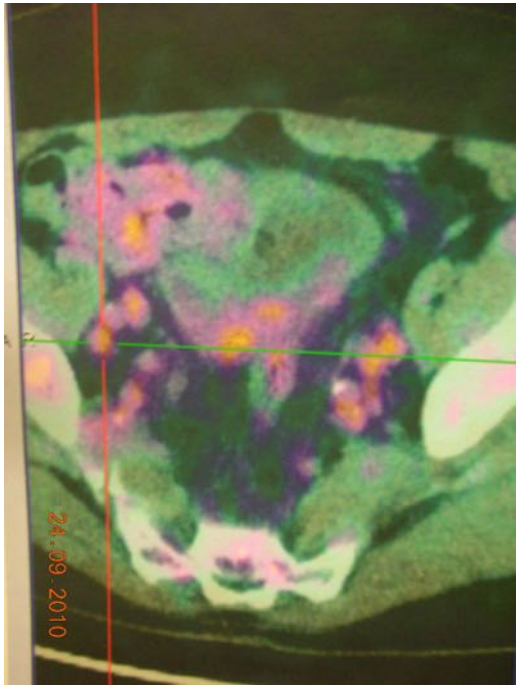
Definition	ADT	Refferring trial
Single High risk	28 months	RTOG 92-02
Multiple High risk or T3b	28-36 months	RTOG 92-02 EORTC 22863
T4 N0 M0 Any T N+ M0 (PSA>150 ng/ml)	At Least 3 years Long Lasting	EORTC 22863 RTOG 85-31

ADT in high risk patients

My personal belongings

- **Always** stage as better as you can





- **Always** use High Dose RT

Conclusion

Radiation Therapy makes difference in PCa

High dose RT improves results, but ADT is still necessary in some patients

Stage patients, in reasonable time, as better as possible before to submit to ADT

Analyze your institutional results

Share and use a patient oriented risk class

Conclusion

ADT + RT in Prostate Cancer:

Type:

LHRH Analogue + Anti-androgen (flair-up)

Timing:

- Neoadj and conc → to improve RT results
- Adjuvant → Systemic control

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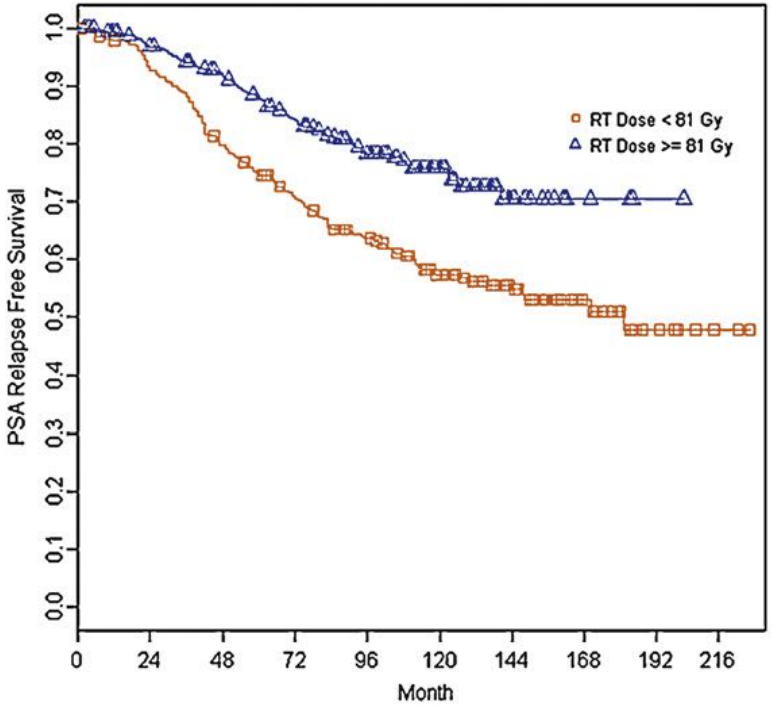
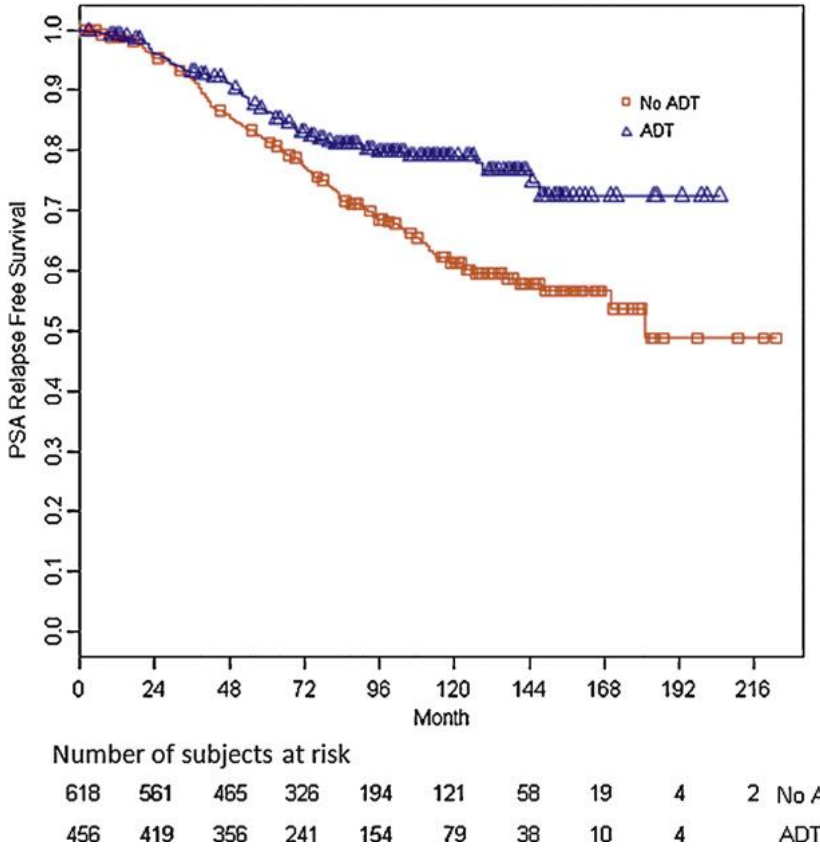
ADT in intermediate risk patients

MSKCC, 2551 pts





Zelefsky MJ et al, Eur Urol 60:1133-1139, 2011